TOXEMIA AND HYPERTENSION DURING PREGNANCY*

THOMAS F. FERRIS, M.D., AND LINDA L. FRANCISCO, M.D.

Department of Medicine
University of Minnesota
Minneapolis, Minnesota

HYPERTENSION may occur during pregnancy because of toxemia of pregnancy, a systemic disease unique to pregnant women in which hypertension is associated with renal disease manifested by proteinuria and reduction in glomerular filtration rate or hypertension may occur without evidence of renal involvement, in which case it is classified as essential or idiopathic hypertension. Proper treatment of the hypertension in either case usually results in a successful pregnancy. In this article, we shall discuss the diagnosis and treatment during pregnancy of toxemia, essential hypertension, and hypertension secondary to other causes.

TOXEMIA

Toxemia is a multisystem disease, typically occurring in late pregnancy, with the usual clinical manifestations of hypertension, proteinuria, edema, and central nervous system irritability. Because convulsions may occur with severe toxemia, the disease has been divided into eclampsia, a term used synonymously for a convulsive disorder until early in this century, and pre-eclampsia, based on whether a seizure has occurred. Toxemia accounts for approximately 70% of hypertension seen in pregnant women.

In a normal pregnancy, despite a 30 to 40% increase in blood volume and cardiac output, arterial pressure falls because of decreased peripheral vascular resistance. The fall in vascular resistance begins during the first trimester and rises slightly during the last four weeks of gestation. The vasodilation of pregnancy is hemodynamically similar to an arteriovenous shunt but the decrease in resistance is not uniform in all vascular beds; blood flow through the kidneys, skin, and uterus is increased but no change has been noted in he-

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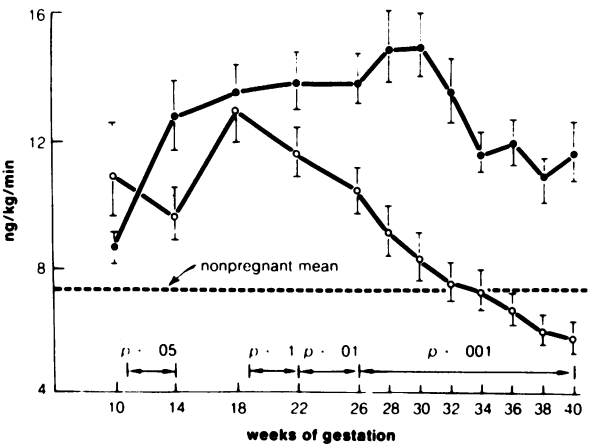
Address for reprint requests: Thomas F. Ferris, M.D., Department of Medicine, University of Minnesota, 420 Delaware Street SE, Minneapolis, MN 55455

patic or cerebral blood flow. The etiology of this fall in peripheral vascular resistance is not known but recent findings suggest that the prostaglandin system may play a role in the control of vascular resistance during pregnancy. Both plasma[1] and urinary prostaglandin E_2[2] are high in pregnancy, as well as plasma 6-Keto prostaglandin $F_{1\alpha}$, the major metabolite of prostacyclin or prostaglandin I_2[3]. Because prostaglandin I_2 is synthesized in all blood vessels and is a vasodilator and antagonist to the vasoconstrictor effect of angiotensin, its increased synthesis might be a factor in the fall in peripheral resistance and angiotensin resistance which occur during pregnancy.

The decrease in vascular resistance during pregnancy has important clinical implications—blood pressure considered normal in nonpregnant women may be elevated in pregnancy. In a large series of pregnant women, mean arterial pressure (diastolic plus one third pulse pressure) was found to be 79 ± 9 mm. Hg at the 22nd week of gestation and rose only to 82 ± 8 mm. Hg by the 40th week.[4] Thus, a blood pressure of 120/80 mm. Hg (mean arterial pressure of 93 mm. Hg) may be an elevated blood pressure during pregnancy. This becomes evident when one looks at fetal mortality which rises when diastolic blood pressure is higher than 84 mm. Hg.[5] Failure of physicians to recognize the new values of normal blood pressure during pregnancy has resulted in failure to detect and to treat toxemia and hypertension in its earliest phase.

The mechanism of the hypertension in toxemia is not clear but, as in all types of human hypertension, peripheral resistance is increased. Resistance to the pressor effect of angiotensin occurs with pregnancy and this insensitivity develops during the first trimester. In women who ultimately develop toxemia a change in sensitivity begins in midpregnancy so that at the time of the clinical onset of toxemia their sensitivity to angiotensin exceeds that of nonpregnant subjects (see figure).[6] In addition, sodium retention associated with toxemia may heighten peripheral resistance by arteriolar swelling. Increased vascular resistance induces exquisite sensitivity to sodium retention.

Alterations occur in the renin-angiotensin and prostaglandin system during pregnancy. Plasma renin and angiotensin levels are high during pregnancy, and renin secretion increases during the first trimester. The cause of the increased renal renin secretion may be an increase in prostaglandin synthesis. Both prostaglandins E_2 and I_2 are known to increase renal renin secretion and synthesis of renin and angiotensin are increased in pregnancy. In addition to increased renin secretion from the kidneys, renin is produced by the uterus of pregnant women and animals.[7]



Variations in angiotensin sensitivity throughout pregnancy. Note the decrease in sensitivity to angiotensin (measured as nanograms of angiotensin/kg./min. needed to raise diastolic pressure 20 mm. Hg) seen as early as the 10th week of gestation. In women who develop toxemia (open circles) a progressive increase in sensitivity begins at the 18th week. With the development of overt toxemia after 32 weeks, sensitivity had increased to levels greater than in nonpregnant women. In women with normal pregnancy (closed circles) a decreased sensitivity to angiotensin persists throughout the pregnancy. Reproduced by permission from Gant, N. F., Daley, G. L., Chand, S., et al.: A study of angiotensin II pressor response throughout primigravid pregnancy. *J. Clin. Invest.* 52:2682-89, 1973.

This synthesis of renin by the pregnant uterus may be important in regulating blood flow in the uterus during pregnancy. Angiotensin has been demonstrated to increase uterine blood flow in pregnant rabbits and dogs;[7] the effect appears to be specific and occurs with nonpressor doses of angiotensin. Angiotensin is known to stimulate renal prostaglandin E_2 synthesis and similarly uterine venous prostaglandin E_2 concentration rises dramatically with angiotensin infusion into the uterine artery.[8,9] Therefore, renin may act in the uterus as a tissue enzyme, regulating uterine blood flow through control of local angiotensin and prostaglandin E_2 synthesis.

Although toxemia is associated with variable concentrations of plasma renin and angiotensin, the increased sensitivity of the peripheral vasculature to angiotensin in toxemia could cause hypertension in the face of a normal or lowered angiotensin II concentration. Whether a similar decrease in uterine renin synthesis might lead to reduction in uterine production of prostaglandin E_2 and a subsequent fall in uteroplacental blood flow in toxemia is not known. Clinical evidence suggests that uterine blood flow is reduced with toxemia and whether the report of decreased synthesis of prostaglandin I_2 in the umbilical and placental blood vessels of toxemic women[10,11] is a factor in the change in uterine flow remains to be determined. It has also been reported

that plasma 6-Keto prostaglandin $F_{1\alpha}$ is lower in hypertensive pregnancies.[12]

In addition to alterations in the renin-angiotensin and prostaglandin systems in toxemia, sodium balance is also deranged. Although edema occurs in up to 75% of normotensive pregnancies because of an enlarged uterus compressing the inferior vena cava, dilatation of venous capacitance vessels, and diminished colloid osmotic pressure in pregnancy, the rapid development of edema with a rise in blood pressure usually marks the onset of toxemia. Because of the frequency of edema in pregnancy, the suggestion has been made that edema be disregarded as a clinical sign of toxemia. This would deny the most important clinical harbinger of the disease. Edema is benign provided vascular resistance remains low. However, the onset of edema and a rise in blood pressure indicates salt retention occurring with diminished vascular capacity. In these circumstances, salt retention becomes a major factor in causing the hypertension. Failure to recognize the significance of edema in the face of a rise in blood pressure prevents early recognition of toxemia. Salt retention not only increases extracellular fluid volume but also increases sensitivity to angiotensin[13] and possibly peripheral resistance by arteriolar swelling.

The cause of sodium retention in pre-eclampsia is most likely reduction in the glomerular filtration rate. Since the renal tubular cells must reabsorb more sodium during pregnancy because of the 50% increase in glomerular filtration rate, a small reduction in glomerular filtration might cause an increase in fractional resorption of sodium. The sodium retention is not due to elevated aldosterone secretion, which usually falls with the onset of toxemia.[14] Indeed, toxemia with edema has been described in patients with Addison's disease maintained on a constant mineralocorticoid dose.[15-17] The renal vasoconstriction which occurs with toxemia may also contribute to salt retention by preventing the normal renal natriuretic response to hypertension.

The fascination of toxemia to investigators interested in hypertension is that it brings into sharp focus the importance of several factors—salt retention, plasma renin and angiotensin, control of sensitivity of angiotensin, and prostaglandin synthesis, all of which play a role not only in toxemia but in all forms of human hypertension.

Much has been made of the reduction in plasma volume that occurs in patients with toxemia. The reduction is variable but averages approximately 9% in the published studies of plasma volume in toxemia.[18] Interestingly, this is the same degree of plasma volume contraction reported by Tarazi et al.[19] in patients with essential hypertension; greater volume depletion is often seen in patients with renal artery stenosis, pheochromocytoma, or malignant hyper-

tension. It reflects constriction of venous capacitance vessels causing increased capillary hydrostatic pressure. Some have unfortunately interpreted the resulting diminished plasma volume and low central venous pressure caused by venous constriction as evidence that toxemia is a volume contracted state to be treated with saline or dextran. Such efforts only increase blood pressure and risk the possibility of life-threatening pulmonary edema or cerebral vascular hemorrhage. The use of volume expansion in toxemia has led Nicholas Assali, an eminent obstetrician who has spent a lifetime studying the pathophysiology of toxemia to state: "These misconceptions would be merely amusing if they did not lead to courses of action that could be devastating to the patient."[18]

Treatment

The first aim of treatment of toxemia should be its prevention. Proper prenatal care with attention to adequate but not excessive weight gain and careful monitoring of blood pressure reduces the incidence of the disease. Nutritional factors have often been cited as important causes of toxemia, but there is no evidence for a nutritional basis for the disease. The World Health Organization Expert Committee has stated, "There seems to be no scientific basis for believing that deficiency or excess of any essential nutrient predisposes to pre-eclampsia and eclampsia."

The most important feature in the prevention and treatment of toxemia is recognition that a rise in blood pressure greater than 30 mm. Hg (systolic) or 15 mm. Hg (diastolic) during pregnancy is significant and that development of proteinuria is always an indication for hospitalization. Using 140/90 mm. Hg as the upper limit of normal blood pressure is without basis in pregnancy. A level of 125/75 mm. Hg before the 32nd week of gestation and 125/85 mm. Hg thereafter is associated with decreased fetal survival and on that basis should be considered abnormal. Although approximately 25% of pregnant women have blood pressures higher than 125/85 mm. Hg during the last month of pregnancy, it is in these women that toxemia is more apt to occur.

The initial therapy for toxemia is bed rest, preferably with the patient lying on her side. Blood pressure, pulse, respirations, and urine volume are carefully monitored. In conscious patients there is no need for an indwelling catheter, but in patients having convulsions or who are comatose, an indwelling catheter is warranted to evaluate urine output. In patients with mild toxemia, i.e., blood pressure no higher than 140/90 mm. Hg, therapy consists of bed rest; sedation with phenobarbital, 50 mg. every six hours, or

diazepam (Valium®), 10 mg. given intramuscularly; salt restriction to 1 to 2 gm. daily; and, if edema is present, 50 mg. hydrochlorothiazide or 40 mg. furosemide orally. These measures usually suffice to control the hypertension. Baseline blood urea nitrogen, creatinine, and uric acid levels are obtained, and 24 hour urine samples collected to determine volume and total protein excretion. Daily weights guide the extent of diuresis. The level of serum uric acid before institution of diuretic therapy is a guide to the severity of the toxemia. A uric acid greater than 4.5 mg./dl. is virtually diagnostic of toxemia and a uric acid above 5.5 mg./dl. indicates severe toxemia. Extremely high levels of uric acid can occur in toxemic patients following a convulsion because intense muscular effort causes elevation of plasma lactate which further decreases uric acid clearance. When hypertension develops during pregnancy without the characteristic renal lesion of toxemia, there is usually no change in the serum urate concentration. Thus, a serum uric acid below 4 mg./dl. in a pregnant hypertensive woman is most consistent with either essential hypertension or toxemia without renal involvement.[20]

If therapy lowers blood pressure to below 120/80 mm. Hg, proteinuria is less than 150 mg./24 hrs., renal function is normal, and there is no evidence of central nervous system hyperexcitability, the patient can be followed weekly as an outpatient if further growth of the fetus is felt to be indicated. If the patient is at term and there is no concern about fetal viability, delivery is indicated as soon as the patient's clinical status is stable.

When a patient has more severe hypertension, i.e., blood pressure greater than 140/90 mm. Hg, more potent antihypertensive therapy should be initiated. Although magnesium sulfate has long been used by American obstetricians, it cannot be considered either a potent antihypertensive or anticonvulsant. Its anticonvulsant effect depends on an effect at the neuromuscular junction where magnesium decreases the amount of acetylcholine released by a given motor nerve impulse. There is no evidence that it affects electroencephalographic evidence of seizure activity. Magnesium concentrations of approximately 3 to 6 mEq./L are considered within the therapeutic range; respiratory failure occurs at higher concentrations. Thus, the disappearance of spinal reflexes with magnesium sulfate is due to the peripheral action of magnesium and indicates a plasma magnesium concentration of approximately 10 mEq./L. Convulsions have been reported to occur with "therapeutic" magnesium concentrations[21] and studies have demonstrated no correlation between cerebrospinal fluid and serum concentrations of magnesium.[22]

Magnesium is also a mild vasodilator and like all smooth muscle relaxants depresses myometrial activity. With the availability of more potent and safer antihypertensive drugs, there is little advantage in using magnesium sulfate other than the experience and confidence American obstetricians have in it.

Hydralazine (Apresoline), a vasodilator, is effective when used in doses of 25 to 50 mg. every six hours orally. To prevent the reflex tachycardia that occurs with hydralazine, propranolol, 40 mg. every six hours, has been effectively combined with hydralazine in the treatment of essential hypertension. Because propranolol does cross the placenta, it may cause fetal bradycardia and mask one indicator of fetal distress. Thus, it has not been used to a great extent in the treatment of acute toxemia, but it and other beta adrenergic blockers have been used throughout pregnancy in women with essential hypertension with excellent results.[3-5] Methyldopa, an adrenergic blocking drug, also blocks the reflex tachycardia caused by hydralazine and may be given orally in doses of 250 to 500 mg. every six to 12 hours.

If the diastolic blood pressure is greater than 110 mm. Hg, parenteral antihypertensive therapy is indicated. Five hundred mg. methyldopa (Aldomet ®) and 40 to 80 mg. furosemide may be given intravenously and repeated every six hours. Since parenteral methyldopa requires six to eight hours for maximum effect, immediate control of blood pressure can be accomplished with parenteral hydralazine. Hydralazine 25 mg. intramuscularly or 25 to 50 mg. dissolved in 50 ml. of 5% glucose in water, intravenously, usually rapidly controls blood pressure. When given intramuscularly, hydralazine requires frequent administration (at least every three to four hours), and constant monitoring of blood pressure is necessary when given intravenously. Its effect is rapid, and like all vasodilators it will increase cardiac output and pulse by reflex sympathetic activity. With severe toxemia, where the diastolic blood pressure is greater than 120 mm. Hg, diazoxide has proven quite effective. Morris et al.[26] treated nine patients with severe pre-eclampsia and three with eclampsia using intravenous diazoxide. Diastolic blood pressure never fell below 50 mm. Hg and significant change in fetal heart rate was observed in only one patient. The only side effect of diazoxide was the cessation of labor in about 50% of the patients, probably as a result of the generalized smooth muscle relaxant effect of the drug. Administration of oxytocic agents immediately restarted labor. Finnerty[27] reported treatment of 61 patients with severe toxemia using diazoxide. Mean arterial pressure fell from 141 mm. Hg to 92 mm. Hg with no maternal deaths and only 4 fetal deaths, an incidence similar to untreated toxemia.

Reluctance of obstetricians to lower blood pressure is based on the

impression that hypertension increases uterine perfusion. Measurements of uteroplacental circulation in toxemia are not possible but studies in pregnant rabbits, using radioactive microspheres to measure uterine blood flow, demonstrate that uterine blood flow is constant over a range of blood pressure from 75 to 120 mm. Hg.[28] Since uterine vasoconstriction may account for the reduction in flow with toxemia, relief of the vasoconstriction may increase perfusion of the uterus, particularly if cardiac output increases. It is known that both hydralazine (Apresoline) and diazoxide increase cardiac output, and methyldopa (Aldomet) reduces blood pressure with little or no change in cardiac output. Diazoxide in pregnant rabbits increases uterine blood flow and in pregnant ewes no change in uterine blood flow occurred following diazoxide when maternal blood pressure did not fall below a mean arterial pressure of 50 mm. Hg.[29] Monitoring revealed no change in fetal pulse even when diazoxide was injected directly into the fetal circulation. In experimental studies of the effect of hypotension on the fetus, one is struck by the tolerance the fetal circulation has to hypotension, a point commented upon by Assali.[30] Because the major cause of maternal mortality in toxemia is cerebral vascular hemorrhage, one must at all costs prevent this catastrophe, and evidence is conclusive that antihypertensive agents prevent cerebral vascular accidents in human hypertension.

After reduction of the blood pressure and the patient's clinical state is stabilized, delivery of the fetus is indicated in severe toxemia. If fetal survival is questionable, the pregnancy may continue provided that blood pressure is controlled and renal function does not deteriorate, but continued hospitalization is required. The patient should be maintained on 1 to 2 gm. sodium diet and diuretics given until edema disappears, at which time they should be discontinued. If elevation of the blood urea nitrogen persists in spite of blood pressure control, delivery is indicated, because fetal growth or maturation are not likely in the presence of azotemia.

In patients with severe toxemia and hyperreflexia, anticonvulsant therapy is indicated. Convulsions always indicate severe disease with increased maternal and fetal mortality and are an indication for delivery. For immediate control of seizures, diazepam (Valium) 5 mg. is administered intravenously and may be continued at a dose of 20 mg. intramuscularly every six hours. The solution should be injected slowly, taking at least one minute for each 5 mg. injected. When using any anticonvulsant, resuscitative equipment should be readily available. Doses of 5 to 10 mg. diazepam intravenously cause mild transitory tachycardia in the mother, but produce no adverse effects on blood pH or pCO_2 in the mother or newborn.[31,32] Transient

hypotonia has been reported in infants with high doses, particularly when given intravenously to the mother, but respiratory depression did not occur.[33-35] Diazepam has been used extensively in India for treatment of toxemia and has gained wide acceptance because its hypnotic and sedative effect seem useful in situations where nursing care is limited.

If convulsions appear imminent, phenytoin 1 gm. in 100 ml. saline may be given intravenously at the rate of 50 mg./min. Plasma levels of the drug can be monitored and should not exceed 18 μg./ml. Although intravenous diphenylhydantoin can cause hypotension and respiratory depression, this adverse effect is minimized if administration of the drug does not exceed 50 mg./min. Patients developing cardiac arrhythmias with intravenous administration have usually had underlying cardiac disease. Diphenylhydantoin does cross the placenta, and in epileptic mothers on both diphenylhydantoin and phenobarbital throughout pregnancy, a neonatal coagulation defect has been reported.[36] The defect responds to vitamin K, which should be given to all infants of mothers treated chronically with anticonvulsants throughout pregnancy. No infants of mothers treated acutely for toxemia with anticonvulsants have been reported to develop this coagulation defect.

Because edema is usually prominent in toxemia, diuretics are logical drugs to use. The argument against their use has been based on two findings. First is the hemoconcentration that may be present in toxemia indicating intravascular plasma volume contraction. As pointed out previously, hemoconcentration is common with all forms of hypertension and is of little clinical significance. The 9% reduction in plasma volume is similar to that found in nonpregnant subjects with essential hypertension. Second, diuretics have been reported to decrease the dehydroepiandrosterone clearance which was developed by Gant et al. to measure uterine blood flow.[37] The clearance of dehydroepiandrosterone depends upon its placental conversion to estrone and estradiol and this has been found to be reduced approximately 50% in toxemia. As pointed out by Clewell and Meschia,[38] dehydroepiandrosterone clearance is not mathematically an acceptable method to measure uterine blood flow. Human uterine and placental blood flow at term is approximately 500 ml./min., but the dehydroepiandrosterone clearance is only 19 ml./min. and in toxemia the clearance falls to a value of 11 ml./min. This clearance may be an indicator of placental function but is not a measure of uterine blood flow. Why it is reduced following diuretics and other antihypertensive drugs, including hydralazine, remains unclear at this time but there has been no correlation between this clearance and fetal survival in any of the published studies.

The largest study of the effect of treatment on fetal prognosis in toxemia was carried out by Friedman and Neff[5] at 14 university hospitals and included data on more than 55,000 pregnant women. Among women with hypertension but without proteinuria they noted no difference in fetal survival when treated with diuretics. However, when hypertension and proteinuria were present, fetal mortality was 1.85% among untreated women compared to 4.43% among women treated with diuretics. However, there was also a significant increase in fetal mortality when any drug, i.e., antihypertensives, narcotics, or anticonvulsants were used. Because the most frequent complication of toxemia is an increase in fetal mortality, these data would be most consistent with an interpretation that with more severe toxemia, fetal mortality is higher and more drugs are used. It does not prove that drugs caused the higher fetal mortality. In several studies[39-42] where diuretics were given throughout pregnancy in an effort to decrease the incidence of toxemia, fetal mortality was no higher among women given prophylactic diuretics. In one series of 604 women, Rauramo et al.[43] instituted treatment with diuretics at the first sign of toxemia, i.e., hypertension or proteinuria and compared the results with a series of patients from the same clinic not treated with diuretics. Severe toxemia developed in 2.3% of the treated women compared to 7.3% in the untreated group and perinatal mortality was 2.3% in the diuretic treated group compared to 4.6% in untreated women. Thus, diuretics are not contraindicated in pregnancy when there is a clinical indication for their use. Because most women with toxemia are edematous, use of diuretics for their natriuretic and antihypertensive effect is quite appropriate.

The definitive treatment of toxemia is delivery of the fetus, but the question of fetal viability precludes immediate delivery in every instance. Measurements of fetal development may be helpful, utilizing urinary estriol and pregnanediol determinations as well as lecithin:shpingomyelin ratios in amniotic fluid.[44] When toxemia is associated with low urinary estriol excretion, intrauterine growth has probably ceased, and delivery of the fetus is indicated. This is probably more feasible today, since neonatal intensive care units allow for optimum care of the premature infant. Delivery by induction of labor or cesarean section can be accomplished. The uterus of a toxemic patient is very responsive to oxytocic agents, and labor is usually short.

Essential Hypertension

Essential hypertension accounts for approximately one third of all hypertension during pregnancy. The history frequently reveals hypertension, dia-

betes mellitus, and obesity among other family members. Women in whom hypertension develops during the second half of pregnancy but who show no other evidence of toxemia (i.e., edema, proteinuria, hyperuricemia) can be regarded as having latent essential hypertension unmasked by pregnancy, and a high proportion of them remain permanently hypertensive after pregnancy.[45-47] No intensive work-up of hypertension during pregnancy is necessary but auscultation of the abdomen to determine if a murmur, suggestive of renal artery stenosis, is present and palpation of the femoral arteries to exclude coarctation of the aorta are indicated. Because pheochromocytoma is associated with high maternal mortality during pregnancy, symptoms suggestive of such a tumor should be elicited.[48] The retina should be examined for evidence of long-standing hypertension, i.e., increased light reflex, arteriolar narrowing, and arteriovenous nicking. An electrocardiogram to determine the presence of left ventricular hypertrophy may also be used as a guide to the chronicity of the hypertension. Retinal hemorrhages and exudates indicate accelerated hypertension, which warrants immediate hospitalization. Baseline serum uric acid levels should be obtained and in hypertensive women without toxemia are usually 4 mg./dl. or less.

Although the prognosis for successful pregnancy in a woman with essential hypertension is excellent, risks of pregnancy are increased in hypertensive women. It may increase the risk of obstetrical complications like premature separation of the placenta and abruptio placenta, it predisposes to the development of toxemia,[49] and myocardial infarction[50] is more apt to occur in hypertensive women during pregnancy if blood pressure is not controlled. The likelihood of toxemia is increased two to sevenfold if there is underlying essential hypertension but essential hypertension generally is associated with an uneventful pregnancy if blood pressure is controlled. Mild essential hypertension generally is associated with uneventful pregnancies and an excellent chance for fetal survival. Pregnant women with hypertension should, therefore, be treated exactly as they would be if they were not pregnant, maintaining blood pressure as close to normal as possible with the use of hypertensive agents.

TREATMENT

Because of the proved efficacy of antihypertensive therapy in preventing complications of hypertension, more women who are taking antihypertensive drugs are being followed through pregnancy. Patients with essential hypertension should have their blood pressure maintained below 140/90 mm. Hg

ANTIHYPERTENSIVE MEDICATIONS IN PREGNANCY

Chronic essential hypertension	*Toxemia*
Diuretics	
Thiazide 1-2 tab. q.d.	Thiazide 1-2 tab. q.d. Furosemide (Lasix) 40 mg. p.o. or i.v.
Central adrenergic blockers	
Methyldopa (Aldomet) 0.5-3 gm. q.d. Clonidine (Catapres) 0.2-2 mg. q.d.	Methyldopa 0.5-2 gm. p.o. q.d. or 0.5 gm. i.v. q.6h.
Alpha adrenergic blocker	
Prazosin (Minipress) 2-20 mg. q.d.	Not used
Beta adrenergic blockers	
Propranolol (Inderal) 20-80 mg. b.i.d. Metoprolol (Lopressor) 100-200 mg. b.i.d. Nadolol (Corgard) 80-300 mg. q.d.	Not used
Arteriolar dilators	
Hydralazine (Apresoline) 25-50 mg. q.i.d.	Hydralazine 25-50 mg. q.6h. p.o. or 10-40 m.g. I.V. q.3h. Diazoxide 300 m.g. I.V.

with whatever antihypertensive regimen is best suited to them. Table I depicts the antihypertensive drugs most often used in women with essential hypertension. Most patients on long term therapy for essential hypertension will be on a combination of either methyldopa and a diuretic or propranolol, hydralazine, and a diuretic. The drugs should be continued throughout pregnancy. In some women reduction of the dose, and, in a few, elimination of medications may be necessary during the pregnancy because of a reduction in blood pressure. However, this should be done only with careful monitoring and the blood pressure should be maintained normal throughout pregnancy. Diuretics should be continued through the pregnancy because significant volume depletion is not present with chronic diuretic administration and their antihypertensive effect is independent of sustained volume depletion. Women receiving chronic diuretic therapy retain sodium normally during pregnancy.

There is recent evidence in pregnant animals that the angiotensin converting enzyme inhibitor, Captopril, reduces uterine prostaglandin E_2 synthesis and strikingly increases fetal mortality.[51] This drug, recently released for the treatment of hypertension, should not be used during pregnancy until more information is forthcoming.

Patients with essential hypertension should be seen every two to three weeks during pregnancy and weekly after the 32nd week. The development

of proteinuria or a rise in blood pressure indicates immediate hospitalization. Although there is no evidence that antihypertensive medication increases urinary estriol excretion, there is evidence that they increase perinatal survival. Leather[52] found in a randomized series of 100 pregnant hypertensive women with diastolic blood pressure greater than 95 mm. Hg prior to the 20th week that antihypertensive therapy with methyldopa and a diuretic was associated with a significantly better fetal outcome. There were no fetal losses in the treated group compared to five fetal losses in the untreated group. Comparable findings were found by Redman[49] in a larger controlled trial of treatment in which diuretics were not used. Birth weights in the treated group were similar to controls and there was no evidence for altered fetal growth in the treated group. The condition of the neonates at birth was similar in both groups. For hypertensive women developing toxemia before the 32nd week, delivery is indicated if urinary estriols are low, because the chance for further fetal growth seems slim. In patients with essential hypertension, ergot preparations are contraindicated; oxytocin, which has little pressor activity, should be used to induce labor.

Maternal mortality in women with essential hypertension during pregnancy is under 1%, and when death does occur it usually is due to a sudden rise in blood pressure with consequent cerebral hemorrhage, acute left ventricular failure, or malignant encephalopathy. These complications can now be prevented with antihypertensive agents, and maternal mortality due to hypertension should be virtually eliminated. A woman with hypertension who develops toxemia does not invariably become toxemic with subsequent pregnancies, but if toxemia occurred early in pregnancy, subsequent pregnancies are more apt to be associated with toxemia.

Malignant hypertension, associated with retinal hemorrhages, exudates, or papilledema developing during the course of pregnancy was an indication for delivery in the past. There was no hope for fetal survival prior to the availability of antihypertensive therapy for malignant hypertension; this may not now be the case although there are insufficient data.

Secondary Causes of Hypertension

Primary aldosteronism (Conn's syndrome). Women with primary aldosteronism have been followed during pregnancy. Biglieri and Slayton[53] reported a woman whose hypokalemia, but not hypertension, disappeared during pregnancy, presumably because of the antagonistic effect of the elevated progesterone of pregnancy on the action of aldosterone. Gordon et

al.[54] found suppression of the usual high plasma renin activity of pregnancy in a woman with primary aldosteronism whose adrenal adenoma was removed in early pregnancy because of extremely high aldosterone secretion. It appears that the hypokalemia of primary aldosteronism may be relieved during pregnancy, but that hypertension persists.

Renal artery stenosis. Women with proved renal artery stenosis have undergone pregnancy, and most develop toxemia.[55] Of the nine patients in Landesman's series, five developed toxemia with exacerbation of hypertension during pregnancy, whereas four developed proteinuria, edema, and hypertension. Although there is evidence in animals that hypertension induced by renal artery constriction improves during pregnancy,[56] hypertension has been induced in pregnant animals with constriction of the renal artery in late pregnancy.[57] The appropriate course would be to maintain blood pressure at normal levels using antihypertensive drugs and to evaluate and possibly operate upon the patient following delivery. Hypertension caused by renal artery stenosis can be treated medically as readily as other forms of hypertension. Although angiotensin I converting enzyme inhibitors are useful in the treatment of renal hypertension, we would consider them contraindicated in pregnancy because of adverse effects on uterine prostaglandin E_2 synthesis and fetal mortality described in pregnant rabbits.[51]

Coarctation of the aorta. Coarctation of the aorta is a rare hypertensive complication of pregnancy and is associated with toxemia.[58,59] Of 10 patients requiring surgical repair during pregnancy, nine had uncomplicated deliveries with living infants. One patient died during her seventh month of pregnancy from an aneurysm of the aorta at the anastomotic site. The major danger to pregnant women with aortic coarctation is aortic rupture because of the cystic medial necrosis often present in the aortic wall. These changes could be stressed by increased cardiac output during pregnancy, increased blood pressure from toxemia, or the strain of labor.

Pheochromocytoma. Pheochromocytoma is a potentially lethal condition during pregnancy and is a form of secondary hypertension that must be diagnosed and treated during pregnancy. It is an extremely rare cause of hypertension during pregnancy and only 93 pheochromocytomas during pregnancy are reported in the English literature.[48,60,61] Symptoms of severe headache, profuse sweating, palpitations, nausea and vomiting, blurred vision, vertigo, tremulousness, seizures, and general weakness are frequently present. Physical findings suggesting hyperthyroidism—tachycardia, lid lag, and fine tremor—should alert the obstetrician to the possibility of a

pheochromocytoma. In pregnant women with pheochromocytomas, the maternal mortality rate is approximately 50%. The cause of death is usually pulmonary edema, cerebral hemorrhage, and cardiovascular collapse. The tumor should be removed surgically during pregnancy once the diagnosis has been established. Concern about the dangers of x-irradiation when localizing the tumor is inappropriate with this potentially lethal condition.

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